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ABSTRACT

Sea-level (SL) residents sojourning at high altitude (HA) experience a metabolic adaptation resulting in reduced muscle glycogen use during submaximal exercise compared to SL exercise of the same duration and percent maximal O_2 uptake (%$\dot{V}O_2$ max). Glycogen-sparing was hypothesized to result from chronic sympathetic nervous stimulation at HA. The present study aimed to determine if beta-adrenergic blockade during HA acclimatization would prevent this metabolic adaptation. Additionally, the study design enabled observation of the combined effects of propranolol and acute high altitude exposure on metabolic responses to submaximal exercise. Twelve unmedicated males exercised (cycle: 80% $\dot{V}O_2$ max) for 30 min at SL (50m) and at HA (4300m) after 3, 8 and 20 days residence. Three days prior to ascent and through day 15 at HA, six men received propranolol (80 mg three times daily) and six received placebo. Propranolol treatment resulted in a reduction in the plasma lactate accumulation during exercise on days 3 and 8 at HA compared to the placebo-treated subjects, but there was no difference in lactate accumulation between the two groups on day 20. Muscle glycogen utilization during 30 min exercise at SL (mean ± SE) was 186 ± 21 mM glucose·kg dry tissue^{-1}. Glycogen utilization on day 20 at HA (119 ± 27 mM glucose·kg dry tissue^{-1}) was unaffected by the previous propranolol regimen but was reduced ($P<0.02$) compared to SL. Post-exercise, plasma ($P<0.01$) and possibly muscle lactate ($P<0.09$) was lower on day 20 at HA than at SL. These data confirm that HA acclimatization results in a decrease in both glycogen utilization and lactate accumulation during submaximal exercise; however, beta-adrenergic blockade did not prevent the glycogen-sparing adaptation. In addition, propranolol reduces plasma lactate accumulation during submaximal exercise at HA, which is the same effect as has been reported at SL.

EFFECT OF PROPRANOLOL ON METABOLIC RESPONSES TO EXERCISE AT HIGH ALTITUDE

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ABSTRACT

Sea-level (SL) residents sojourning at high altitude (HA) experience a metabolic adaptation resulting in reduced muscle glycogen use during submaximal exercise compared to SL exercise of the same duration and percent maximal O_2 uptake (%$\dot{V}O_2$ max). Glycogen-sparing was hypothesized to result from chronic sympathetic nervous stimulation at HA. The present study aimed to determine if beta-adrenergic blockade during HA acclimatization would prevent this metabolic adaptation. Additionally, the study design enabled observation of the combined effects of propranolol and acute high altitude exposure on metabolic responses to submaximal exercise. Twelve unmedicated males exercised (cycle; 80% $\dot{V}O_2$ max) for 30 min at SL (50m) and at HA (4300m) after 3, 8 and 20 days residence. Three days prior to ascent and through day 15 at HA, six men received propranolol (80 mg three times daily) and six received placebo. Propranolol treatment resulted in a reduction in the plasma lactate accumulation during exercise on days 3 and 8 at HA compared to the placebo-treated subjects, but there was no difference in lactate accumulation between the two groups on day 20. Muscle glycogen utilization during 30 min exercise at SL (mean ± SE) was 186 ± 21 mM glucose•kg dry tissue^{-1}. Glycogen utilization on day 20 at HA (119 ± 27 mM glucose•kg dry tissue^{-1}) was unaffected by the previous propranolol regimen but was reduced ($p<0.02$) compared to SL. Post-exercise, plasma ($P<0.01$) and possibly muscle lactate ($P<0.09$) was lower on day 20 at HA than at SL. These data confirm that HA acclimatization results in a decrease in both glycogen utilization and lactate accumulation during submaximal exercise; however, beta-adrenergic blockade did not prevent the glycogen-sparing adaptation. In addition, propranolol reduces plasma lactate accumulation during submaximal exercise at HA, which is the same effect as has been reported at SL.

Key Words: Acclimatization, Altitude, Hypoxia, Exercise-Metabolism, Catecholamines, Environmental Adaptation, Beta-Adrenergic Blockade

INTRODUCTION

During exercise, the metabolic rate is determined by the absolute intensity or power output. However, the relative proportion of energy obtained from carbohydrate versus fat oxidation is determined by the relative exercise intensity defined as the oxygen uptake ($\dot{V}O_2$) expressed as a percent of the individual's maximal oxygen uptake ($\dot{V}O_2$ max). Thus, two individuals exercising at different absolute power outputs will have different $\dot{V}O_2$, but if the $\dot{V}O_2$ represents the same % $\dot{V}O_2$ max for each, then the amount of muscle glycogen depletion will be approximately equal (20). Furthermore, an aerobic training program which increases an individual's $\dot{V}O_2$ max will decrease muscle glycogen utilization during prolonged submaximal exercise compared to exercise at the same absolute power output before training. However, pre- and post-training exercise bouts at the same % $\dot{V}O_2$ max (i.e., higher absolute power output post-training) will result in an equal amount of glycogen depletion (20). At high altitude, $\dot{V}O_2$ max is reduced compared to sea level, thereby providing the opportunity to study the effect of changing the relationship between absolute and relative intensity in the opposite direction from that achieved by physical training.

Previously, it was reported that muscle glycogen utilization during thirty minutes of exercise at 85% $\dot{V}O_2$ max was the same with acute (<2 hours) high- altitude (4,300 m) exposure as at sea level (29). The reduction in $\dot{V}O_2$ max with acute altitude exposure required that absolute power output be reduced proportionately to maintain % $\dot{V}O_2$ max the same during exercise bouts at high altitude as at sea level. Thus, with acute high-altitude exposure, the relationship between the % $\dot{V}O_2$ max and rate of muscle glycogen depletion appears the same as would be predicted based on results of physical-training studies at sea level. However, after 18 days of continuous residence at 4300 m, there was a reduction in the amount of glycogen utilized during the thirty-minute exercise bout as compared to sea level (29). Unlike the glycogen sparing effect of physical training at sea level, there were no associated changes in either $\dot{V}O_2$ max (29) or in glycolytic or oxidative skeletal muscle enzyme activity (30)

during the period of altitude acclimatization. The glycogen sparing adaptation observed at altitude was attributed to a greater free fatty acid mobilization and utilization during exercise. It was hypothesized that this metabolic shift from carbohydrate to fat oxidation resulted from the effects of chronic stimulation of the beta-adrenergic sympathetic nervous system. Sympathetic nervous activity is known to be increased at high altitude (14).

The purpose of the present investigation was to test the hypothesis that chronic beta-adrenergic sympathetic nervous stimulation was responsible for the glycogen-sparing effect of altitude acclimatization. The approach used to test this hypothesis was to determine if administration of propranolol to healthy sea-level residents during their initial period of acclimatization at high altitude would prevent the development of the glycogen sparing adaptation. In addition, the design of the investigation allowed the combined effects of propranolol and high altitude on exercise metabolism to be studied. Propranolol is a widely prescribed medication which acts as a nonspecific beta-blocking agent (25). The effects of propranolol on cardiorespiratory (21,22,27) and metabolic (18) responses to exercise at sea level have been well studied, but propranolol effects on metabolic responses to exercise at high altitude have not been investigated.

METHODS

Subjects and Experimental Design. The subjects for this study were 12 healthy males ranging in age from 19 to 23 years. They volunteered after being completely informed regarding risks and requirements of participation. The subjects were not receiving any regular medication. All were lifelong lowland residents who had not sojourned at high altitude for at least six months prior to this investigation. Descriptive characteristics (mean $\pm$ SE) of the subjects were: 176 $\pm$ 3 cm; body mass, 76 $\pm$ 3 kg; maximal O_2 uptake ($\dot{V}O_2$ max) determined using a discontinuous cycle protocol at sea level, 3.64 $\pm$ 0.14 $\ell \cdot min^{-1}$. The subjects were assigned to

two groups approximately matched for physical fitness. One group was then randomly designated as the CONTROL ($\dot{V}O_2$ max = 3.47 ± 0.19$\ell \cdot min^{-1}$), and the other served as the EXPERIMENTAL group ($\dot{V}O_2$ max = 3.76±0.25$\ell \cdot min^{-1}$). At sea level (Natick, MA: 50m), the unmedicated subjects all completed $\dot{V}O_2$ max testing followed three days later by a 30-min submaximal (80% $\dot{V}O_2$ max) exercise test. After completing these procedures, the subjects initiated a medication program which continued for three days at sea level, at which point they were rapidly (< 8 hours) transported to the summit of Pikes Peak, CO (4300 m) where they resided continuously for 20 consecutive days. The medication regimen was continued uninterrupted through the fifteenth day of residence at high altitude. The subjects repeated the 30-min submaximal exercise test on the third and eighth day of residence at 4300 m. Two days (days 16 and 17 at 4300 m) following discontinuation of medication were allowed for clearance of the drug. On the eighteenth day at 4300 m, the $\dot{V}O_2$ max was determined. On the twentieth day of altitude residence, the subjects repeated the 30-min submaximal exercise test. Absolute exercise intensity for the submaximal exercise tests at high altitude was adjusted lower than at sea level in order that relative intensity be 80% of the $\dot{V}O_2$ max determined at 4300 m.

The medication regimen for the EXPERIMENTAL group consisted of 80 mg three times daily of oral propranolol (Ayeret Laboratories) for a total dose of 240 $mg \cdot day^{-1}$. The CONTROL group received a matching placebo (lactose). The subjects were not informed as to who was receiving propranolol and who received placebo.

Experimental Procedures. All exercise was performed on a mechanically-braked cycle ergometer (Monark) with the subjects pedaling at a rate of 60 rpm. An electronic metronome was used to assist the subjects to maintain the correct pedaling frequency and the exact pedal rate was determined by an observer counting revolutions every minute during maximal exercise testing and every fifth minute during submaximal exercise testing. A discontinuous protocol of progressively increasing

power output was used to determine $\dot{V}O_2$ max (12), and the criterion for accepting a $\dot{V}O_2$ as maximum was that a 30 watt increase in intensity be accompanied by an increase in $\dot{V}O_2$ of less than 150 $ml \cdot min^{-1}$. For submaximal exercise, a target $\dot{V}O_2$ corresponding to 80% $\dot{V}O_2$ max was calculated for each individual and an initial power output to elicit that $\dot{V}O_2$ was estimated using data from Astrand (2). The exercise intensity was adjusted as needed, based on the $\dot{V}O_2$ measured at the fifth minute of the submaximal test, and no further adjustment in intensity was made thereafter. During all exercise, oxygen uptake, carbon dioxide output and minute ventilation were determined at intervals of 30 sec ($\dot{V}O_2$ max tests) or 1 minute (submaximal tests) using an automated system which has been described in detail previously (15). Heart rate was determined from the electrocardiogram obtained from bipolar electrodes (CM-5) at the same intervals as respiratory measurements.

Prior to and immediately at the completion of the submaximal exercise at sea level and on day 20 of residence at 4300 m, vastus lateralis muscle samples were obtained by biopsy; note that the subjects were unmedicated on both of these occasions. Muscle samples for lactate analysis were frozen within several seconds of the biopsy by plunging the entire needle into liquid N_2; the post-exercise muscle sample for lactate analysis was frozen 5-10 sec after exercise stopped. Muscle tissue for determination of pre- and post-exercise glycogen concentration was obtained from a second "pass" through the same incision, divided into several pieces, cleaned of blood and connective tissue, and the weight of each piece, corrected for water evaporation (7), was determined. All tissue was then frozen and stored for subsequent analysis in liquid N_2. Prior to metabolite analysis, all muscle samples were freeze-dried (VIRTIS Freeze-Drier) and the dry weight was determined. The wet-to-dry weight ratio was calculated for each tissue sample. Enzymatic-fluorometric techniques were used for determination of both muscle lactate (6) and glycogen (19) concentrations. Muscle samples for lactate were analyzed in triplicate. Muscle glycogen was determined in triplicate in two or three pieces of tissue, and the triplicate values of each piece

averaged to give a single value for the sample. In this report, muscle metabolite concentrations are expressed relative to the dry weight.

For all the submaximal exercise bouts, venous blood samples were obtained immediately before, and five min after completion. Blood samples were obtained from a catheter placed in the antecubital vein thirty minutes before exercise and kept patent by slow infusion 0.9% NaCl. Additionally, twice at sea level and on days 3, 8 and 20 at 4300, catheters were emplaced prior to the subject arising in the morning and fasting blood samples obtained 30 min later. Blood samples were collected in EDTA and an aliquot was assayed for lactate concentration within 30 minutes. The remaining blood was separated into plasma, aliquoted and frozen in liquid N_2 until aliquots were analyzed in triplicate for free fatty acid (16), glycerol (3), glucose (Beckman automated analyzer), insulin (SIGMA radioimmunoassay kit), norepinephrine and epinephrine (5) concentration.

The data were analyzed using multifactor analysis of variance (ANOVA) for repeated measures. As will be discussed, one CONTROL subject did not complete the exercise bouts on days 3 and 8 at high altitude, therefore his data was not included in the ANOVA of the plasma metabolite data. He did complete the tests in which biopsies were performed, therefore his data was included in ANOVA of muscle glycogen and muscle lactate data. Significance of factor main effects and multifactor interaction effects was determined for the following factors: group (EXPERIMENTAL versus CONTROL); exercise (pre- versus post-exercise); altitude (sea level versus days 3, 8 and 20 at high altitude). When factor main effects or multifactor interactions were found to be statistically significant ($P<0.05$), Neuman-Keuls procedure was used to determine the location of significant differences between means. All data are reported as the mean $\pm$ SE. Cardiorespiratory data collected during the maximal and submaximal exercise bouts have been presented and discussed in detail elsewhere (15) and therefore will be discussed in this report only to the extent that they pertain to the metabolic responses.

RESULTS

TABLE 1 ABOUT HERE

Table 1 shows the power output, $\dot{V}O_2$, % $\dot{V}O_2$ max and heart rate of the subjects at the end of the steady-state exercise bout. At sea level, there were no differences between the groups in power output, $\dot{V}O_2$ or % $\dot{V}O_2$ max during exercise. As described previously (15), the $\dot{V}O_2$ max at 4300 m was lower than at sea level, and the decrement in CONTROL and EXPERIMENTAL subjects was the same. The absolute power outputs were reduced for the submaximal exercise bouts at altitude to offset the reduction in $\dot{V}O_2$ max and maintain the relative exercise intensity the same as at sea level. There were no significant differences in relative intensity between groups. The respiratory exchange ratio after 25 min of submaximal exercise was also unaffected by group or altitude, averaging 0.98 overall. At sea level, one subject from the EXPERIMENTAL group became exhausted after 18 min of exercise, but the remaining subjects all completed the full 30 min. One subject from the CONTROL group did not perform the submaximal exercise bout on the 3rd and 8th day at altitude due to an injury. Of the remaining 11 subjects, only three from each group completed the full 30 min of exercise on day 3; two CONTROL and one EXPERIMENTAL subject stopped after 10 min while the two remaining EXPERIMENTAL subjects stopped after 15 and 20 min, respectively. Although all the EXPERIMENTAL subjects and three CONTROL subjects completed the entire 30 min exercise bout on day 8 at 4300, two CONTROL subjects were still unable to continue exercising beyond the 10th min. All subjects completed the entire 30 min of submaximal exercise on day 20 at 4300 m.

FIGURE 1 ABOUT HERE

The pre- and post-exercise plasma catecholamine concentrations of the subjects at sea level and at high altitude are shown in Figure 1. Norepinephrine

concentrations (Figure 1A) in both the CONTROL and EXPERIMENTAL subjects increased ($P<0.01$) with exercise at sea level and on all three of the test days at high altitude. Both pre- and post-exercise norepinephrine concentrations were greater ($P<0.01$) on the eighth and twentieth day at high altitude than at sea level. Catecholamine analysis of blood samples obtained from the subjects after a 10-hour fast and prior to their arising from bed in the morning (data not shown) also indicated that there was an increase ($P<0.05$) in basal levels of circulating norepinephrine by the eighth day at altitude. Analysis of variance indicated that there were no significant differences in norepinephrine concentration between CONTROL and EXPERIMENTAL groups. However, the interaction effect of "group" and "exercise" factors bordered on statistical significance ($P<0.12$), probably reflecting the tendency, apparent in Figure 1A, for a smaller increment in norepinephrine concentration with exercise on day three at altitude in the EXPERIMENTAL as compared to CONTROL subjects. With one exception, mean epinephrine concentrations did not differ with exercise, altitude or between groups; the mean epinephrine concentration of the CONTROL subjects following exercise on day three at altitude was higher than all other values. The epinephrine concentrations in the blood samples obtained from the fasted subjects prior to their arising in the morning were unchanged by altitude and did not differ between groups. As has been previously reported (15), the propranolol dosage regimen effectively maintained blood propranolol concentration of 65-108 $ng \cdot ml^{-1}$ in EXPERIMENTAL subjects during the treatment period.

FIGURE 2 ABOUT HERE

Figure 2 shows pre- and post-exercise plasma metabolite concentrations at sea level and high altitude. Plasma lactate concentration (Figure 2A) increased ($P<0.05$) during all of the exercise bouts. Post-exercise plasma lactate concentrations in both groups of subjects were lower on days 8 and 20 at high altitude compared to sea

level. On day three at high altitude, post exercise lactate concentrations of the CONTROL subjects were not different from sea-level values. Post-exercise lactate concentrations of the EXPERIMENTAL subjects on day three at high altitude were lower ($P<0.08$) than those of the CONTROL subjects, and were reduced ($P<0.01$) relative to sea-level values. Plasma glucose (Figure 2B) and glycerol (Figure 2C) concentrations both increased ($P<0.01$) during the exercise bouts, but neither were affected by altitude exposure nor were there any differences between the two subject groups in glucose or glycerol concentrations. Post-exercise plasma free fatty acid concentrations were lower in the EXPERIMENTAL than CONTROL subjects on day 3 at high altitude, but there were no other differences in the free fatty acid concentrations of the two groups. Resting plasma free fatty acid concentrations (Figure 2D) were unchanged by altitude exposure. Plasma free fatty acid concentrations increased ($P<0.05$) during exercise at sea level and at high altitude on day 20, but not on days three or eight, when post-exercise free fatty acid concentrations were lower ($P<0.05$) than at sea level. Between days 8 and 20 at high altitude, there was a large increase in post-exercise plasma free fatty acid concentration. Resting plasma insulin concentrations at sea level did not differ between CONTROL (12.9 ± 4.2 μ units$\cdot ml^{-1}$) and EXPERIMENTAL (13.3 ± 4.9 μ units $\cdot$ ml^{-1}) subjects, and insulin levels were not significantly affected by exercise or altitude exposure.

TABLE 2 ABOUT HERE

Muscle glycogen concentration of both groups before and after the 30 min submaximal exercise bouts at sea level and at high altitude on day 20 are shown in Table 2. Glycogen utilization was calculated for each individual by subtracting post-exercise glycogen concentration from the pre-exercise value. There were no significant differences among pre-exercise muscle glycogen concentrations due to altitude or group.

There were no significant differences between CONTROL and EXPERIMENTAL subjects in glycogen utilization during exercise, either at sea level or on day 20 at high altitude. Glycogen utilization was less ($P<0.02$) during exercise on day 20 at 4300 m compared to sea level. There were no significant differences between CONTROL and EXPERIMENTAL subjects in muscle lactate concentrations at rest or following exercise. Muscle lactate increased ($P<0.01$) with exercise at both sea level and high altitude on day 20. There appeared to be a trend ($P<0.09$) for lower muscle lactate concentrations following exercise at altitude (1.5 ± 0.7 mmol$\cdot$kg^{-1} dry tissue) as compared to sea level (2.7 ± 0.7 mmol$\cdot$kg^{-1} dry tissue). However, individual muscle lactate accumulation (pre-exercise minus post-exercise) was calculated, and no significant difference between sea level and high altitude was found.

DISCUSSION

Propranolol is extensively prescribed for the treatment of hypertension and various cardiac abnormalities. Its pharmacological action is to nonselectively block $beta_1$- and $beta_2$-adrenergic receptors (25). Because of this pharmacological property, propranolol was used in this study to investigate the importance of chronic sympathetic nervous stimulation for adaptations in exercise metabolism which have been observed to occur in healthy person during the first few weeks of altitude acclimatization (29). As noted previously (15), an increasingly large number of persons are engaging in various types of strenuous activity (e.g., skiing, hiking) at high altitude, and many of these individuals may be undergoing propranolol treatment. Therefore, the results of this study may have both basic physiological and practical clinical significance. Propranolol effects on cardiorespiratory responses to exercise during altitude sojourn have already been reported elsewhere (15), and herein the effects on metabolic responses to exercise at altitude are considered.

In agreement with other reports (4), the unacclimatized subjects of this investigation experienced an increase in sympathetic nervous activity during the sojourn

as indicated by the increase in basal levels of circulating norepinephrine (See Figure 1A). Propranolol had no effect on this adrenergic activation at high altitude. This observation is in agreement with the findings of Svedenhag (24) that resting norepinephrine concentrations of healthy subjects at sea level were unaffected by eight weeks of propranolol treatment. Furthermore, intravenous administration of propranolol prior to exercise at sea level has little effect on the increment in plasma norepinephrine with exercise (8). The results of this investigation indicate that this is probably also the case at high altitude. The possibility, however, that propranolol blunts the sympathetic nervous response to exercise at high altitude cannot be ruled out. There was a tendency for the increment in plasma norepinephrine to be greater in placebo than propranolol-treated subjects during exercise on day 3, although not on days 8 or 20 at high altitude. Interestingly, however, the placebo-treated subjects also exhibited an increase in plasma epinephrine during this exercise bout indicating activation of the adrenal medulla. Thus, the greater increment in norepinephrine in the placebo-treated subjects may be due to a greater secretion by the adrenal medulla. Possibly, the tachycardia during exercise, which was prevented by the propranolol, contributed to the placebo-treated subjects' overall level of anxiety during exercise.

The hypothesis of the present investigation was that beta-adrenergic blockade with propranolol during the acclimatization period would prevent the glycogen-sparing adaptation. Clearly, this was not the case, since the primary observation of the present study was that both placebo-treated subjects and those treated with propranolol for the first 15 days of altitude acclimatization utilized less muscle glycogen during the exercise bout on day 20 at 4300 m than at sea level. One possible explanation is that plasma propranolol levels were not maintained sufficiently high enough for effective beta-blockade. The propranolol dosage employed in this investigation was 240 $mg \cdot day^{-1}$ (80 mg TID), which effectively maintained plasma propranolol levels between 65-108 $mg \cdot \ell^{-1}$. The medication regimen was initiated three days before ascent to altitude to ensure effective beta-blockade upon first arrival

through the fifteenth day at 4300 m when the medication was stopped. As reported elsewhere (15), this propranolol dosage was sufficient to reduce heart rate during submaximal and maximal exercise by about 40-45 $b \cdot min^{-1}$ (day 3 at altitude), and withdrawal of the drug was followed by an increase in heart rate during exercise. Svedenhag et al. (24) have employed a propranolol dosage (160 $mg \cdot day^{-1}$) similar to that used in this study, and reported preventing certain metabolic adaptations (increases in mitochondrial oxidative capacity) normally resulting from an eight-week training program at sea level. Saven et al.(21) reviewed a number of studies performed at different altitudes reporting the effects of beta-blocking agents on physical training and suggested that beta-blockade might exert an even more potent effect at high altitude than at sea level. Animal studies also indicate that sensitivity to a given dose of propranolol is increased by hypoxia (14). Thus, the medication regimen appears to have been sufficient to satisfactorily maintain effective beta-adrenergic blockade.

In contrast to the hypothesis, both control and experimental subjects exhibited a reduction in glycogen utilization during exercise on day 20 at high altitude as compared to sea level. In fact, the data (Table 2) suggest the possibility that glycogen utilization may have decreased even more in the propranolol treated subjects than in control subjects, although differences between the groups were not statistically significant. Both groups of subjects experienced an increased sympathetic nervous activity at high altitude as evidenced by increased circulatory norepinephrine levels. Although there was a tendency for the propranolol treated subjects to experience a small increment in norepinephrine during exercise on day 3 at altitude, circulating levels under basal conditions were not different between groups. It is possible that following propranolol withdrawal there was sufficient time for beta-adrenergic stimulation to produce the adaptation. Propranolol treatment at sea level results in an increased beta-receptor density which persists for more than 48 hours following withdrawal of the drug (17), and this effect is potentiated by high circulating

norepinephrine levels (17). Perhaps the increased beta-receptor sensitivity (density) combined with high norepinephrine levels accelerated the adaptive process following withdrawal of propranolol high altitude. This possibility cannot be discounted. However, the failure of propranolol treatment to prevent the glycogen-sparing effect of altitude acclimatization strongly suggests that this adaptation does not result from chronic beta-adrenergic stimulation.

In the previously reported study (29), the glycogen sparing effect associated with altitude acclimatization was inferred to have occurred as a result of an increase in the mobilization and utilization of fatty acids as a substrate during exercise. This conclusion was based on the observed effect of acclimatization on changes in plasma glycerol and free fatty acid concentrations during exercise. The data from the present investigation are not as clear. There was an increase in post-exercise plasma free fatty acid concentrations on day 20 as compared to day 8 at high altitude suggesting greater fatty acid mobilization; however, the post-exercise fatty acid levels were not significantly greater than sea-level values. Also, the ratio of the molar concentrations of plasma free fatty acids and glycerol decreased during exercise (indicative of an increase in utilization of fatty acids relative to mobilization), but there was no difference in the change in the ratio between sea level and day 20 at high altitude. The explanation for this apparent discrepancy between these data and those of other studies indicating an increased reliance on fat metabolism during exercise at high altitude may be related to maintenance of higher resting muscle glycogen levels in the subjects of the present study. Sutton et al. (23) have questioned whether a shift to fat metabolism is an effect of altitude acclimatization per se, or rather the effect of the low carbohydrate/hypocaloric diet often assumed by altitude sojourners due to anorexia or ration restrictions. The results of the present investigation tend to support the latter. Unlike the previous study (29), resting muscle glycogen levels in the present investigation were not lower at the end of the altitude sojourn than at sea level. Although the subjects in this study consumed an ad libitum diet, they

were strongly encouraged to consume a high carbohydrate diet particularly during the last five days at high altitude preceding the biopsy experiment. Dietary records were not kept, but the staff members themselves prepared and served most of the meals consumed during the final days of the sojourn, and maintenance of muscle glycogen at sea-level values is attributed to this emphasis on carbohydrate in the diet at altitude. This remains to be verified in a carefully controlled dietary study.

If neither chronic beta-adrenergic stimulation nor increased mobilization and utilization of fat are requisite for the glycogen-sparing effect of altitude acclimatization, then what is the underlying mechanism? The reduction in glycogen utilization (Table 2) during exercise on day 20 at high altitude compared to sea level appears also to have been associated with a reduction in lactate production. Blood flow to the exercising muscle on day 20 at high altitude would be expected to be lower than at sea level. An increase in arterial oxygen content occurs after about ten days of altitude acclimatization (9), and, at sea level, an increase in arterial oxygen content has been shown to produce a concommitant reduction in muscle blood flow for a given oxygen uptake (26). A reduction in muscle blood flow with no change in muscle lactate production would result in an increased muscle lactate concentration. In fact, post-exercise muscle lactate concentration on day 20 at high altitude was the same or lower ($P<0.10$) than at sea level, therefore lactate formation must have been reduced. This suggests that the metabolic rate which can be sustained aerobically is increased (in terms of % $\dot{V}O_2$ max) by altitude acclimatization despite the fact that $\dot{V}O_2$ max is relatively unchanged during the first three weeks at high altitude (15,29). In support of this concept are the previously reported data indicating that the anaerobic threshold is increased durng the first three weeks of residence at 4300 m (28). Acclimatization may result in cellular adaptations facilitating pyruvate decarboxylation and increased flux through the tricarboxylic acid cycle, thereby increasing the energy yield of glycolysis. Alternatively, neuromuscular recruitment pattern may be altered by acclimatization such that there is an increased reliance on oxidative muscle fibers during exercise at high altitude.

This is the first investigation in which propranolol effects on metabolism during exercise have been evaluated at high altitude. On day three at high altitude, post-exercise plasma lactate concentrations of propranolol- treated subjects were lower than placebo-treated subjects. In humans performing prolonged exercise at sea level, beta-adrenergic blockade with propranolol has been reported to reduce blood lactate accumulation (11). The authors of that study speculated that this effect was due to an increased pyruvate oxidation secondary to a reduction in beta-oxidation of fatty acids and citrate accumulation, rather than a direct inhibition of muscle glycogenolysis, since there had been no effect of propranolol on muscle glycogen depletion (11). Lipolysis and mobilization of free fatty acids during exercise are impaired by beta-adrenergic blockade with propranolol at sea level (8,10). In the present investigation, propranolol treatment did not appear to inhibit lipolysis during exercise on day three at altitude since glycerol concentrations increased with exercise, and there were no differences in post-exercise plasma glycerol between the two groups. Post-exercise plasma free fatty acid concentrations were lower in propranolol than placebo-treated subjects, raising the possibility that increased oxidation of free fatty acids enabled a reduction in carbohydrate oxidation. Alternatively, the oxygen affinity of whole blood (but not dialyzed hemoglobin solutions) is decreased in the presence of propranolol, albeit at concentrations (0.5 mM) somewhat higher than the plasma propranolol concentrations (0.2 to 0.4 mM) measured in the present study (1). If this effect occurs in vivo, the lower plasma lactate concentrations in the propranolol-treated subjects could be due to facilitation of oxygen delivery to the muscle. Unfortunately, muscle biopsies were not performed in conjunction with the exercise tests during the medication period, so changes in muscle glycogen and lactate concentrations are unknown, and these speculations remain to be investigated.

Two out of five CONTROL and three out of six EXPERIMENTAL subjects failed to finish the full 30 min of submaximal exercise on day three at 4300 m; average exercise times were the same (22 min) for both groups. On the eighth day

at altitude, all propranolol-treated subjects completed 30 min of exercise, but two of five placebo-treated subjects were still unable to finish due to exhaustion. As reported elsewhere (15), the decrement in $\dot{V}O_2$ max at high altitude was the same for both groups. Therefore, propranolol did not appear to exert any greater effect on performance capacity than already imposed by altitude, and the difference in lactate responses to exercise was a direct effect of propranolol, not differences in exercise duration.

In summary, the following observations were made concerning muscle metabolism during exercise at high altitudes: 1) beta-adrenergic blockade does not prevent the glycogen-sparing adaptation associated with altitude acclimatization; 2) increased mobilization and utilization of free fatty acids is not necessarily the mechanism allowing the glycogen-sparing effect of altitude acclimatization; and 3) plasma lactate accumulation during prolonged submaximal exercise at high altitude is reduced by propranolol treatment the same as at sea level. These findings combined with those of the previous report (15) indicate that propranolol does not potentiate the decrement in physical performance of healthy sea-level residents sojourning at high altitude. Whether or not these findings hold true for hypertensive or cardiac patients remains unknown.

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FIGURE LEGENDS

Figure 1. The change in plasma norepinephrine (NE) and epinephrine (E) concentration with 30 min exercise (80% $\dot{V}O_2$ max) at sea level and high altitude.

Figure 2. The change in plasma lactate, glucose, glycerol and free fatty acid concentrations with 30 min exercise (80% $\dot{V}O_2$ max) at sea level at high altitude (4300 m).

Table 1. Exercise intensities and cardiorespiratory responses during steady-state exercise.

	Control Subjects (n=5)				Experimental Subjects (n=6)			
	Sea Level	Time on Pikes Peak Day 3	Day 8	Day 20	Sea Level	Time on Pikes Peak Day 3	Day 8	Day 20
Watts	186 ±9	141 ±11	141 ±11	133 ±9	206 ±13	142 ±11	142 ±11	145 ±9
$\dot{V}O_2$ (ml/min)	2740 ±127	2221 ±178	2202 ±186	1998 ±124	2984 ±136	2023 ±141	2290 ±138	2207 ±91
% $\dot{V}O_2$ max	79 ±3	88 ±3	87 ±3	79 ±2	80 ±3	80* ±2	91 ±2	84 ±3
HR ($b \cdot min^{-1}$)	179 ±5	175 ±3	171 ±3	164 ±4	175 ±2	122* ±6	122* ±6	166 ±2

Values are mean ± SE of power output, oxygen uptake ($\dot{V}O_2$), relative exercise intensity (% $\dot{V}O_2$ max) and heart rate; *significantly ($P<0.05$) different from CONTROL subjects.

Table 2. Muscle glycogen utilization during 30 min submaximal exercise.

	Glycogen concentration, mmol glucose•kg^{-1} dry tissue					
	SEA LEVEL			HIGH ALTITUDE, Day 20		
	Pre-Exercise	Post-Exercise	Utilization	Pre-Exercise	Post-Exercise	Utilization
CONTROL	403±49	205±22	198±37	397±34	253±34	144±42•
EXPERIMENTAL	409±31	236±29	174±17	324±30	229±25	95±28•
POOLED	406	220	186	360	241	121•

Values are means ± SE. Pooled is average of values from both CONTROL and EXPERIMENTAL subjects; •Significantly ($P<0.05$) different from sea level.

FIG 2

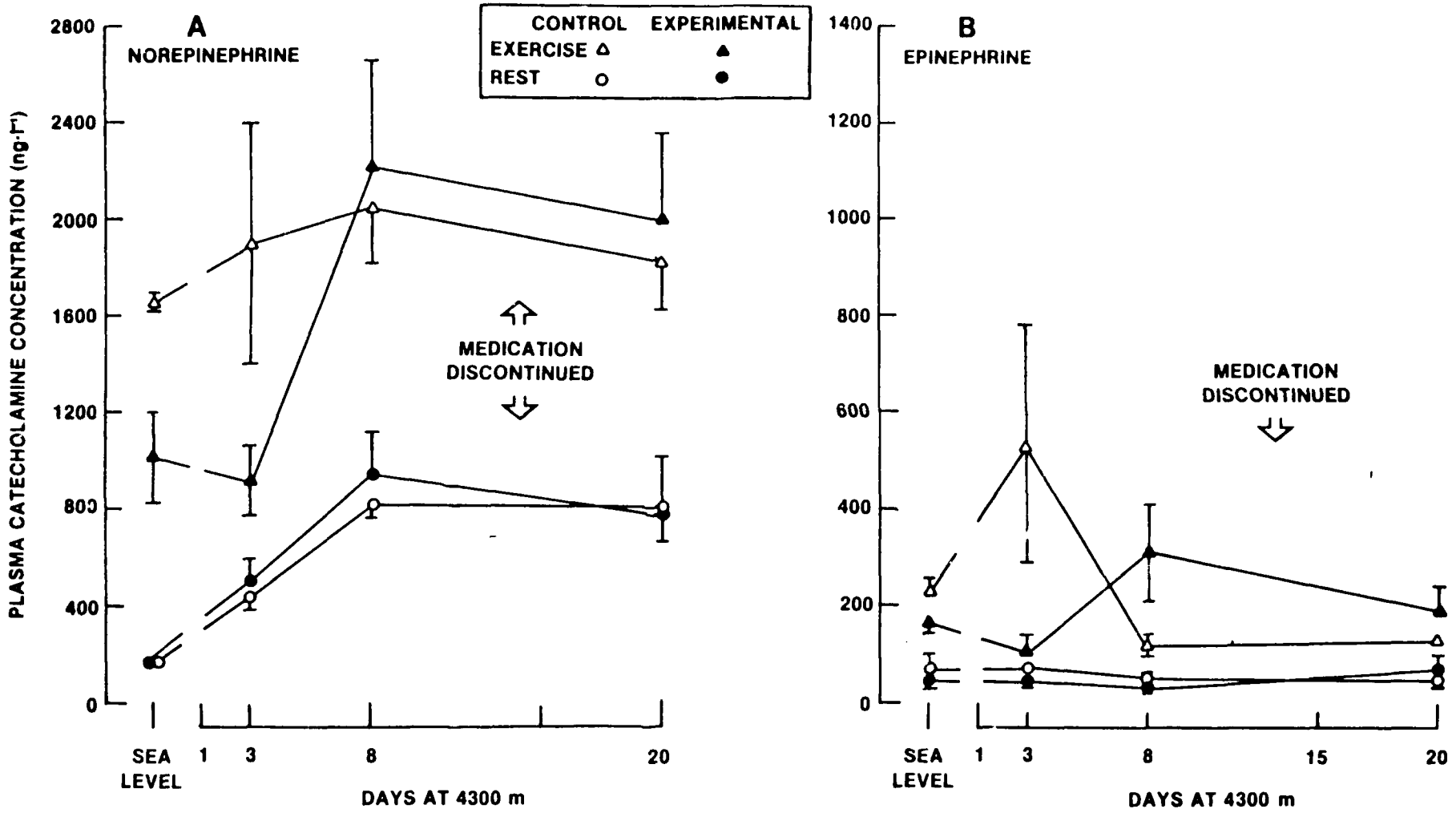
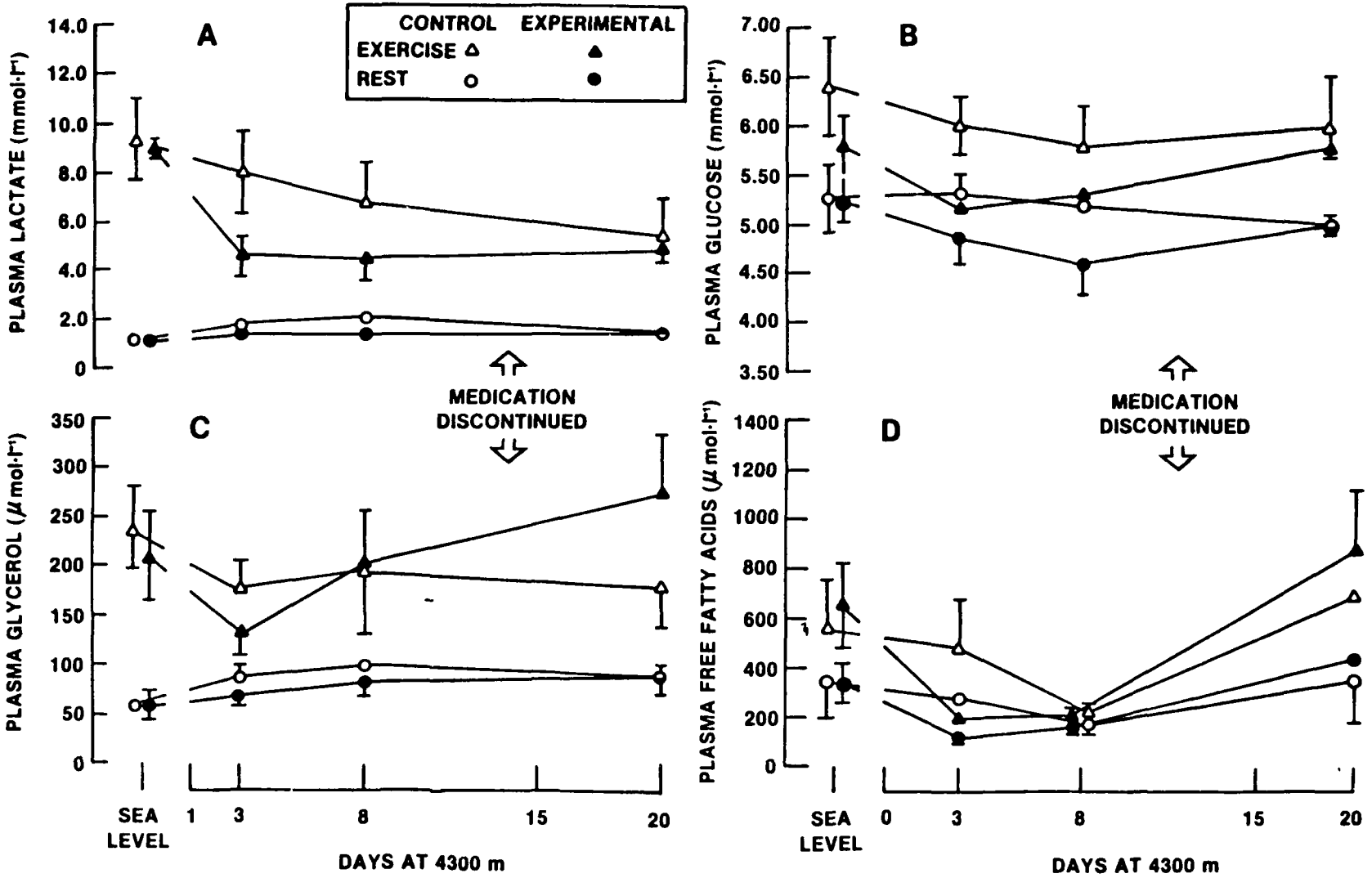

A
NOREPINEPHRINE
CONTROL
EXPERIMENTAL
EXERCISE
REST
MEDICATION DISCONTINUED
PLASMA CATECHOLAMINE CONCENTRATION (ng·l⁻¹)
2800
2400
2000
1600
1200
800
400
0
SEA LEVEL
1
3
8
20
DAYS AT 4300 m
B
EPINEPHRINE
1400
1200
1000
800
600
400
200
0
MEDICATION DISCONTINUED
SEA LEVEL
1
3
8
15
20
DAYS AT 4300 m

FIG 2


CONTROL EXPERIMENTAL
EXERCISE △ ▲
REST ○ ●
A
B
C
D
PLASMA LACTATE (mmol·l⁻¹)
PLASMA GLUCOSE (mmol·l⁻¹)
PLASMA GLYCEROL (μmol·l⁻¹)
PLASMA FREE FATTY ACIDS (μmol·l⁻¹)
MEDICATION DISCONTINUED
SEA LEVEL
DAYS AT 4300 m